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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/723,478	11/25/2003	Mavis D. Adam	PC10973B	7919

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PFIZER INC.
PATENT DEPARTMENT, MS8260-1611
EASTERN POINT ROAD
GROTON, CT 06340

EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 12/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/723,478	ADAM ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-15 and 19-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *19-22* is/are allowed.

6)☒ Claim(s) *1 and 3-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 10/122,698.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12172004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 3-15 and 19-22 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 3-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the preparation of compound of formula (I) and corresponding pharmaceutically acceptable salt thereof, does not reasonably provide enablement for a solvate or polymorph of the compound of formula (I). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination.

The instant claim recites "A compound ... **salts** or **polymorphs** thereof" wherein there is insufficient description in the specification regarding the types of 'solvates' and 'polymorphs' intended by the recitation.

The explanation provided for the term "**solvates**" is as hydrates (see page 7, lines 33-34), however, there is no working example of **solvate** or hydrate of compound of formula (I); and some of the exemplified compounds within the claimed genus were in contact with solvent. Yet they have not formed solvate as evident form spectral data provided for these compounds.

Searching the pertinent art in the related pyridine area did not result in support for such solvates of instant pyridine compounds. Searching the more general area of solvates resulted in pertinent reference West applied below. West clearly shows lack of predictability of the art in the solvate area.

Further, the specification does not provide any explanation of what types of '**polymorphs**' are intended, how these are made, etc. The existence, structure and the properties (e.g., stability, solubility, bioavilability, rate of dissolution, etc.) of polymorphs tend to be very unpredictable. In order to establish the most stable polymorphic form, each has to be characterized and screened individually using various analytical techniques such as X-ray diffraction, thermal analysis, particle morphology characterization, etc. In view of the lack of direction provided in the specification regarding the starting materials, the lack of working examples and the general unpredictability of chemical reactions, it would take an undue amount of experimentation for one skilled in the art to make the claimed compounds and therefore practice the invention. The starting material sources necessary to obtain the instant compounds must have been available as of the filing date in order to provide an enabling disclosure. See *In*

re Howarth, 654 F.2d 103, 210 USPQ 689 (CCPA 1981); *Ex parte Moersch*, 104 USPQ 122 (POBA 1954).

Based on the facts above, a scope of enablement rejection follows using relevant Wands factors. Hence, the burden of establishing the *prime facie* case is met with.

Wands analysis for scope of enablement rejection:

1. **The nature of the invention and the state of the prior art:**

The invention is drawn to compound of formula I, or a pharmaceutically acceptable salt, solvate or polymorph thereof. Specification is not adequately enabled as to how to make solvate or polymorph of compounds of formula (I) Specification has no example of solvate of the instant compounds. Specification on page 7 recites that 'solvates of the compounds of the invention include hydrates thereof' but there is no enabling disclosure of such hydrates or solvates. There is no explanation provided regarding what types of polymorphs are intended and how to prepare the same.

The structural formula (I) is drawn to pyridinyl compounds substituted with variable groups R^4, $-CH_2-NR^1R^2$ and –O-(X,Y,Z substituted phenyl). Careful calculation of the number of compounds embraced in the instant formulae shows a large number of compounds. The term "substituted" embraces undefined number of variable groups and thus, the genus embraced by claims is excessively large and there is no teaching of any solvate of this large genus.

Search in the pertinent art, including water as solvent resulted in a pertinent reference, which is indicative of unpredictability of solvate formation in general. The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase

is defined in the second paragraph on page 358 of West (Solid State Chemistry). The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is the compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stabile region of the solvate. In the instant case of solvate a similar reasoning therefore apply. Water is a solvent and hence it is held that a pertinent detail of West, which relates to solvates, is also applicable to water.

In addition, an additional search resulted in Vippagunta et al., Advanced Drug Delivery Reviews 48: 3-26, 2001, which clearly states that formation of solvates in unpredictable. See entire document especially page 18, right column section 3.4. Note Vippagunta et al., states "Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for series of related compounds".

Regarding polymorphs, the reference provides that "The main challenge in managing the phenomenon of multiple solid forms of a drug is the inability to predict the number of forms that can be expected in a given case. This prediction would involve quantification of the myriad intermolecular forces within any proposed crystal structure as well as the ability to postulate the likely packing modes for a given molecule in all its configurations" (see page 11, col. 2).

2. **The predictability or lack thereof in the art:**

Hence the solvate or polymorph as applied to the above-mentioned compounds claimed by the applicant are not art-recognized compounds and hence there should be adequate enabling disclosure in the specification with working example(s).

3. **The amount of direction or guidance present:**

Examples illustrated in the experimental section are limited to making the compounds not related to solvates or polymorphs. There is no example of solvate of instant compound. Many of the exemplified compounds were shown in the specification that have come in contact with water and/or other solvent but there is showing that these compounds formed solvates. Hence it is clear that merely bringing the compound and water or solvent together does not result in solvate and additional direction or guidance is needed to make them - specification has no such direction or guidance.

4. **The presence or absence of working examples:**

There is no working example of any solvate or polymorph formed. The claims are drawn to solvate, yet the numerous examples presented all failed to produce a solvate or even solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "[T]he specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there, is no evidence that such compounds exist... the examples of the patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds

actually exist; if they did, they would have formed. Hence, there should be showing supporting that solvates of these compounds exists and therefore can be made.

5. **The breadth of the claims & the quantity of experimentation needed:**

Specification provides no support, as noted above, for compounds generically embraced in the claims would lead to desired solvate or polymorph of the compound of formula (I). As noted above, the genus embraces a large number of compounds and hence the claims are extremely broad. The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired solvate or polymorph of compound of formula (I) embraced in the instant claims in view of the pertinent reference teachings.

Applicant's arguments filed on December 17, 2004 have been fully considered. Applicant argues that the specification provides enablement for the term "polymorphs". Applicant first cites an online FDA publication to support the arguments that 'different polymorphs of a drug substance are regarded as the same active ingredient'. However, the publication appears to indicate to evaluate the situation on a case by case basis, see page 13, "if the active ingredient of a proposed generic drug product were to have a different polymorphic form that the active ingredient in the reference listed drug, and this difference affected the behavior or certain characteristics of the drug product, then FDA might not approve the generic drug product ....". The reference indicates that every case must be evaluated on the information provided in the disclosure and the in the instant application, there is no guidance or direction to one of ordinary skill in the art, in the preparation of polymorphs of the claimed compounds.

Further, see Vippagunta reference (enclosed herewith) which teaches that there are different types of polymorphism. The reference provides that "There are many limitations in using computational methods for predicting polymorphs theoretically" (see page 12, col. 1). In the absence of preparation methods and working examples, the recitation of the terms "polymorphs" and "solvates" in the instant claims is an invitation to undue experimentation.

Applicant further argues that 'the specification teaches procedures to prepare exemplary polymorphs' and relies on Examples 35 and 38 to provide the same. However, these examples are not seen to provide the type of polymorph prepared and the corresponding diffraction data to support the argument that the prepared compound is in polymorphic form. The reference relied upon to show the 'common methods for the production of solids in the pharmaceutical industry' teaches that "Although it is by now obvious that control of crystal formation is of extreme importance, this control is not always easy to achieve" (see page 15). The reference thus provides each case has to be evaluated based on the fact situation. Further, Byrn et al. (reference cited by applicant in response filed on December 17, 2004) teaches various "analytical problems" associated with the development of polymorphs due to the formation of mixtures of different forms (see page 948). Rovin et al. (cited by applicant) provides that "A thorough understanding of the physical-chemical properties of the new-drug substance under study provides the development pharmacist with data that are essential in designing stable and efficacious dosage forms" (see page 1450). The references collectively teach the importance of providing the undue burden on the skilled artisan to prepare a particular form of the compound. In the absence of proper direction and guidance, there tends to be undue burden on the skilled artisan.

Further, applicant cites many U.S. Patents as state of the art references having claims to polymorphs, however, the references do not conclusively provide to one of ordinary skill in the art to prepare the polymorphs for the instant compounds. As provided above, it is a challenge to predict the number of forms that can be expected in a given case (see Vippagunta, page 11). Further, evidence for enablement in each application must be evaluated on the record developed, to the extent any error has been made in the rejection or issuance of claims in a particular application, the examiner is not bound to repeat that error in subsequent applications. The U.S. Court of Customs and Patent Appeals held, *In re Waite and Allport*, 77 USPQ 586, "[w]e apprehend that there is no rule of patent law more firmly settled, nor any which has been more frequently stated, than the rule that this court will not allow rejected claims simply because similar claims may have been allowed by tribunals of the Patent Office in some other application, or even in the particular application under consideration. *In re Lee et al.*, 31 CCPA (Patents) 768, 139 F2d 717, 60 USPQ 202; *In re Haller*, 34 CCPA (Patents) 1003, 161 F2d 280, 73 USPQ 403".

Claim 15 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a therapeutic method of treating premature ejaculation, does not reasonably provide enablement for a method of preventing the same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. (The reasons provided in the office action in parent application 10/122,698 are incorporated here by reference).

The scope of the method claim 15 is not adequately enabled solely based on their ability to inhibit the uptake of serotonin by human serotonin transporters, provided in the specification. The use disclosed in the specification is as pharmaceutical therapeutic agents having ability to inhibit the uptake of serotonin, useful to treat or **prevent** diseases, including premature ejaculation. Test procedure and assay for measuring the inhibitor potency is provided at pages 96-98 along with generalized IC_{50} values for some of the exemplified compounds, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the prevention of premature ejaculation. There is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

The instant claim recites 'treating or **preventing**', and therefore, the instant claim language embraces disorders not only for the treatment, but for "prevention" which is not remotely enabled. Based on the serotonin re-uptake inhibitory activity, the instant compounds are disclosed to be useful in the "prevention" of premature ejaculation, for which applicants provide no competent evidence. "To prevent" actually means *to anticipate* or *counter in advance, to keep from happening etc.* (as per Websters II Dictionary) and therefore it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the '**preventive**' effect. It is inconceivable from the *in vitro* data of a small number of representative compounds can be correlated to the '**prevention**' of the various claimed disorder, such that the claimed compounds

can not only treat but also "prevent" a myriad of diseases associated with the stated activity. Further, there is no evidence on record which demonstrates that the *in-vitro* screening test relied upon is recognized in the art as being reasonably predictive of success in any of the contemplated areas of 'preventing'. Such a reasonable correlation is necessary to demonstrate such utilities. See *Ex parte Stevens*, 16 USPQ 2d 1379 (BPAI 1990); *Ex parte Busse et al.*, 1 USPQ 2d 1908 (BPAI 1986) (the evidence must be accepted as "showing" such utility, and not "warranting further study").

The state of the art is not indicative of any SRI agents for prevention of premature ejaculation in general. Further there are no known preventative agents for premature ejaculation. Steggall et al., a récent article on premature ejaculation provides that the condition is being treated with SSRIs, however, the article does not provide that the agents are used in preventing. The article provides that 'current definitions of premature ejaculation are difficult to deploy clinically'. Motofei, a state of the art reference (enclosed herewith) provides that 'studies show a serotonergic involvement in premature ejaculation (PE)', however, the reference indicates, that "An effective treatment with SSRIs of PE cases is rather difficult". While the state of the art references indicate a therapeutic treatment of PE using SSRIs, there is no indication of any preventive method or approach of the claimed condition. This clearly establishes that many factors need to be evaluated prior to administering SSRI drug therapy in normal individuals in the expectation of **preventing** premature ejaculation. The examiner notes, there is not seen sufficient guidance provided in the form of administration profiles, combination ratios of the active agents or references to same in the prior art to provide the skilled artisan with sufficient guidance to practice the instant preventive method. Prevention is seen to encompass

administering the active agent to a normal and healthy subject, and noting the fact that symptoms of the claimed condition never manifests itself. The data and evidence provided in the instant disclosure leads the examiner to doubt the objective truth of assertions of prevention of the claimed condition.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to make and/or use the invention commensurate in scope with the claims.

The cited U.S. Patent documents (which according to the applicant, provides the nexus between SSRIs and premature ejaculation) are fully considered, however, these documents are seen to provide a basis for a therapeutic treatment of the condition using the active compound but not seen to accomplish the prevention of the same.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite "any one of claims 1-13" which includes the 'canceled claim 2'

and thus, the claims improperly depend from a canceled claim. Appropriate amendment would obviate the rejection.

Allowable Subject Matter

Claims 19-22 are allowed. The references of record do not teach or fairly suggest the claimed compounds.

Receipt is acknowledged of the Information Disclosure Statement filed on December 17, 2004 and a copy is enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deepak Rao
Primary Examiner
Art Unit 1624

December 12, 2005